REMARKS

Claim 7, 10, 12, 14-18, 20, 22-25 and 30-38 are currently pending. Claims 12, 14, 22, 23 and 32-38 have been withdrawn from consideration. However, Applicant notes that in the event that claim 7 is allowed, claims 12, 14 22, 23 and 32-38 would be subject to rejoinder in view of MPEP 821.04(b) which states:

> ..if applicant elects a claim(s) directed to a product which is subsequently found allowable, withdrawn process claims which depend from or otherwise require all the limitations of an allowable product claim will be considered for rejoinder.

In the present circumstance, claim 7 is directed to a product claim. Claims 12, 14, 22, 23 and 32-38 are directed to methods of using the claimed product.

A. Claims 7, 10, 15-18, 20, 24, 25, 30 and 31 Comply With the Written Description Requirement

In the Office Action dated May 14, 2008, the Office Action stated:

> Claim 7, with dependent claims 10, 15-18, 20, 30 and 31, has been amended on March 3, 2005 and August 29, 2005 and claim 24, with dependent claim 25, was added on March 3, 2005 and amended on August 29, 2005 to recite "wherein a sequence segment comprising 41738-9502 of SEQ ID NO:4 encodes human mouse double minute 2 homolog depicted in SEQ ID NO:2, ... a region comprising a dinucleotide of the following group: 41739-41738, ... ". Applicant does not indicate and the examiner is unable to locate adequate support in the specification for such positions in SEQ ID NO:4, *i.e.* 41738-9502 and 41739-41738. Thus there is no indication that the specific segment of 41738-9502 of SEQ ID NO:4, i.e. said specific positions in SEQ ID NO:4 were within the scope of the invention as conceived by Applicant at the time the application was filed.

In response, Applicant asserts that there is more than adequate support in the specification for claims 7, 10, 15-18, 20, 30 and 31 and in particular, the sequence segment 41738-9502. First, Applicant notes that page 4, lines 25-30 states:

> The invention is directed to isolated genomic polynucleotide fragments that encode ...human mouse double minute 2 homolog, which in a specific embodiment are...human mouse double minute 2 homolog genes, as well as vectors and hosts containing these

> fragments and polynucleotide fragments hybridizing to noncoding regions, as well as antisense oligonucleotides to these fragments.

Further, the specification on page 14, lines 29-33 states:

> The present invention also relates to nucleic acid constructs comprising a polynucleotide sequence containing the exon/intron segments of the .....human mouse double minute 2 homolog gene (nucleotides 1-51039 of SEQ ID NO:4).

Table 2 on page 10 of the specification shows "exon/intron organization of the human mouse double minute 2 homolog gene... in SEQ ID NO:4, 51039 base pairs; nucleotides 99541-150579 in the genomic clone of accession no. AC025423 (reverse strand cloning)". Exon 1 according to Table 2 begins at nucleotide 40646 of SEQ ID NO:4 and the stop codon terminates at nucleotide 10091 of SEQ ID NO:4. Clearly, nucleotides 41738-9502 of SEQ ID NO:4 would constitute a sequence segment that encodes human mouse double minute 2 homolog protein.

Further, there is support for the recitation "a region comprising a dinucleotide of the following group: 41739-41738". In particular, Applicant notes that page 9, lines 29-32 states:

> The invention is further directed to polynucleotide fragments containing or hybridizing to noncoding regions of the ...human mouse double minute 2 homolog genes. These include but are not limited to an expression control element, an intron, a 5'non-coding region, a 3'-non-coding region and splice junctions (see Tables 1-2, as well as transcription factor binding sites (see Table 3).

A region encompassing the dinucleotide 41739-41738 would be within the 3'-noncoding region and would thus constitute a fragment containing a 3'non-coding region.

In conclusion, there is adequate support for the phrase in claim 7 "wherein a sequence segment comprising 41738-9502 of SEQ ID NO:4 encodes human mouse double minute 2 homolog depicted in SEQ ID NO:2, ... a region comprising a dinucleotide of the following group: 41739-41738, ... ". Further, there is adequate support for claim 24 directed to an isolated nucleic acid molecule 20-5000 nucleotides in length consisting of a reverse or forward strand of a contiguous exon-intron region or intron-exon region between nucleotides 41738-9502 of SEQ ID NO:4 and claim 25 directed to "an isolated nucleic acid molecule 20-5000 nucleotides in length comprising nucleotides 41739-41738....". Further, claims 10, 15-18, 20, 24, 25, 30 and 31 ultimately depend from claim 7. Thus, arguments made with respect to claim 7 would apply to these claims as well. Therefore, Applicant respectfully request that the rejection under 35 USC 112, written description be withdrawn.

B. The Rejection Under 35 USC 103

Claims 7, 10, 15-18, 20, 24, 25, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muzny et al. in view of Vogelstein et al. The Office Action states:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to use said cDNA taught by Vogelstein et al. to identify the genomic DNA that encodes the human MDM2 homolog of SEQ 1D NO:2 on chromosome 12. The motivation is provided by Vogelstein et al. who teach that it binds to oncogene p53 and is diagnostic of tumorigenesis (e.g., column 3, lines 20-35). The state of the art provides various techniques for obtaining genomic DNA using cDNA probes that are usually labeled. The comparison of genomic and cDNA would result in the identification of regions comprising exon-intron and intron-exon junctions within coding and noncoding regions. One of ordinary skill in the art would have been motivated to use said non-coding regions or fragments thereof of at least 20 nucleotides and up to 5000 or 51039 nucleotides (the entire length of SEQ ID NO:4) nucleotides for detecting splice variants of the genomic DNA encoding human MDM2 homolog in genomic nucleotide samples from an individual, for example. As a matter of convenience a non-coding region such as an exon-intron or intron-exon region or fragments thereof can be present in a kit or on a solid support. Further, said support can be a microarray according to a customary use of nucleic acid molecules in the art.

Applicant respectfully traverses the rejection. The cDNA disclosed by Vogelstein for the most part just contains coding regions of the MDM2 gene, just a small proportion of the entire genomic sequence. It is not clear as to whether there would be a reasonable expectation of success. The teachings of the subject application provide significant advances in the knowledge of the gene in terms of defining exons, exon sequences, placements of introns, intron sequences and specific control elements that reveal the transcription factors that can act on the gene and the locations of transcription factor binding sites. None of this new information could have been predicted or deduced from mere inspection of the sequences of the genomic clone or cDNA. Further, Applicant questions whether it was standard techniques as of the filing date of the above-referenced application to obtain and identify noncoding sequences only having cDNA and large genomic fragments.

Further, even assuming *arguendo* that there was a motivation to combine the two references, one of ordinary skill in the art would not have obtained the claimed sequences.

Specifically, Applicant notes that Vogelstein placed the human MDM2 homolog gene at 12q12-14. After publication of Vogelstein, the MDM2 homolog gene was found to be located several base pairs away at 12q15. Thus, Applicant would have looked in the wrong place. It is possible under such circumstances that Applicant would have been uncertain as to how to proceed.

In response to arguments made in the Appeal Brief submitted on March 2, 2008, the Examiner stated in the instant Office Action:

> ....Appellant asserts that there would not be a reasonable expectation of success of obtaining the claimed noncoding sequences of SEQ ID NO:4 in view of the cited references. Vogelstein placed the human MDM homologue gene at 12q12-14. As noted above, there was actually a previous disclosure stating that the MDM2 was located between 12q14.3-15 (see, for example, Andersen et al., 1996, Mammalian Genome 7:780-783 and Bureau, 1995, Genomics 28: 109-112, submitted and disclosed in previous response attached hereto as Exhibit 1). However, given the conflicting locations published as of the priority, one of ordinary skill in the art would not have known which location was actually correct" (Brief, page 14).
>
> This is not agreed with because the actual location does not matter as long as it is a part of the Muzny sequence, which it is. Applicant did not need to separate the Muzny sequence into the fragments containing different arms of chromosome 12. In fact, Applicant did not isolate the fragment 12q12-14 or 12q14.3-15. He run cDNA against the genomic DNA disclosed by Muzny and found the location of the gene where it was. This experiment was performed according to the knowledge and the state of the art as evidenced by Watson et al. Watson et al teach that "once the first genes were cloned, introns were identified by comparing the cloned genomic DNA with the corresponding cloned cDNA" ("Recombinant DNA", page 137, 2nd column, form PTO-892 mailed 4/16/07). Applicant's argument would be convincing if the exact location would need to be known before the comparison of the genomic and the cDNA is made. This is not the case because the work is done on the genomic DNA that is known without fragmentation thereof. Applicant further argues that "Watson would not apply in this case since in Watson, the genes themselves were actually cloned" (ibid, page 18, last sentence). This is not persuasive because Muzny provided the piece of the genomic DNA containing the requisite gene. Having the cDNA, it does not require undue experimentation to identify the fragment of the genomic DNA corresponding to the gene and exon-intron locations within said gene.

Applicant disagrees with the assertions made. In Applicant's view, the actual location does indeed matter given the size of the Muzny clone (150,579 nucleotides). How would one of ordinary skill in the art be able to determine the location, size and number of coding and noncoding regions given only the information provided by Muzny and Vogelstein? The possibilities would be infinite. Furthermore, the Watson reference is of limited relevance. As indicated in the legend to Figure 8-2, the structure of, for example, the ovalbumin gene by comparing the genomic DNA and cDNA was not determined until the gene structure was examined by electron microscopy of DNA-mRNA hybrids. Specifically the legend states:

> DNA containing the gene for ovalbumin was hybridized with ovalbumin mRNA. The regions of the gene that hybridized to the mRNA are eight exons..Genomic DNA that encodes introns does not hybridize to the mRNA but forms seven loops..The upper portion of the figure shows the actual electron micrograph. Regions where genomic DNA hybridized to mRNA form a thick line than do the single-stranded genomic DNA loops. The locations and lengths of the introns were estimated simply by plotting the position of each loop along the mRNA molecule. Because the length of the mRNA (in nucleotides) was known, the approximate positions of the introns could be calculated. The middle portion of the figure shows the interpretation of the electron micrograph. The 5' and 3' ends of the mRNA are indicated. The bottom portion shows a scheme of the structure of the ovalbumin gene determine subsequently by DNA sequence analysis of the exon-intron boundaries in genomic DNA and comparison with the cDNA sequence.

One of ordinary skill in the art reading Watson et al. would conclude that it would be necessary to do electron microscopy of genomic DNA and mRNA hybrids **before** comparing cDNA and genomic DNA in order to have an idea of the location of the intron-exon boundaries. Simply comparing cDNA and genomic DNA given the teaching of Watson would not be sufficient.

The Office Action further states:

> The second type of Applicant's arguments concerns with the fact that the cDNA constitutes only 1.6% of the genomic DNA. While the large quantity of the experimentation may be involved, it is not undue because the sufficient guidance and knowledge are provided by the art.

Applicant, as previously argued, respectfully disagrees. As conceded in the Office Action, the MDM2 cDNA constitutes only 1.6% of the genomic DNA. However, this cDNA clearly is not in only one place. However, one of ordinary skill in the art given the disclosures of Muzny and

Vogelstein would not have any idea as to how the cDNA sequences are interspersed. The possibilities are infinite and thus undue experimentation would be involved.

In view of the above arguments, Applicant asserts that the rejections under 35 USC 103 have been overcome. Therefore, Applicant respectfully requests that the rejections be withdrawn.

7. Conclusion

In view of the foregoing, Applicant assert that the claims are now in condition for allowance. Early action to that end is respectfully requested. The Examiner is invited to contact the undersigned at (914) 712-0093 if she has any questions.

Respectfully submitted,

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